PRESYNAPTIC ACTIONS OF NICOTINE IN THE CNS

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Nicotine stimulates the release of neurotransmitters in the CNS. One locus of its action is directly on the nerve terminal, through presynaptic nicotinic acetylcholine receptors. The nicotinic stimulation of dopamine release from striatal nerve terminals has been particularly widely studied. Nicotine acts in a dose-dependent manner (EC_{50}=4μM) to elicit Ca^{2+}-dependent dopamine release. The pharmacological profile of this action shows that other nicotinic agonists such as cytisine and DMPP can also evoke transmitter release, and their action can be blocked by antagonists such as dihydroβerythroidine and mecamylamine; the neuromuscular nicotinic antagonist αbungarotoxin is without effect. This pharmacology favours a ganglionic type of nicotinic receptor, but nicotine-evoked dopamine release is sensitive to agents such as histrionicotoxin that block the integral ion channel of muscle nicotinic receptors, suggesting a common mechanism in the brain receptors. Molecular biological techniques have revealed several isoforms of nicotinic receptors in the CNS. The pharmacological specificity of nicotine-evoked transmitter release is consistent with the involvement of the receptor class identified by high affinity [^{3}H]nicotine binding. This correlation is also supported by the loss of such binding sites following degeneration of pathways after lesion experiments or in degenerative diseases. Subcellular fractionation expermients have shown an abundance of [^{3}H]nicotine binding sites associated with isolated nerve terminals (synaptosomes). Thus the presynaptic localisation of nicotinic receptors may constitute a major proportion of nicotine's target sites in the brain.

The high affinity binding of [^{3}H]nicotine suggests that these nicotinic receptors may rapidly desensitize, with conversion to a high affinity state. Desensitization is seen at the presynaptic receptor in the diminishing responses to successive applications of micromolar concentrations of nicotine. Desensitization is believed to underlie the well-documented increase in numbers of [^{3}H]nicotine binding sites that accompanies chronic nicotine administration. This receptor upregulation was also produced in rats by chronic infusion of the nicotinic agonist anatoxin-a. <u>In vitro</u> assessment of receptor function, by measuring nicotine-evoked dopamine release, indicated that the increased number of binding sites was accompanied by a parallel increase in receptor function. This implies that recovery from desensitization had occurred. Thus nicotine receptors in the brain may be delicately balanced between activatable and desensitized states.

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